

REMARKS

Claims 8-11, 18, and 19 are pending in the present application.

At the outset, Applicants wish to thank Examiner Shippen for the helpful and courteous discussion with their undersigned Representative on April 28, 2005. During this discussion, several amendments and arguments were discussed to distinguish the present invention from that of the prior art. The content of this discussion is reflected in amendments and remarks set forth herein. Reconsideration of the outstanding rejections is requested.

The rejections of Claims 12, 13, and 15-17 under: **(a)** 35 U.S.C. §102(b) over US 4,308,404, US 4,391,997, or US 4,400,555, each optionally in view of US 5,777,180, **(b)** 35 U.S.C. §103(a) over US 5,780,690 or JP 10-175898, each optionally in view of US 4,391,997 and US 4,400,555, and **(c)** 35 U.S.C. §103(a) over US 4,308,404, US 4,391,997, or US 4,400,555, each optionally in view of US 5,777,180, are obviated by amendment.

Claim 8 provides a process for producing bisphenol A comprising condensing phenol and acetone in the presence of, as a catalyst, an acid type ion exchange resin which is modified in part with a sulfur-containing amine compound, wherein:

- (i) said condensing is performed in reaction equipment which comprises at least two reactors in series,
- (ii) said ion exchange resin has a modification rate in the range of 26 to 65 mol%,
- (iii) the methanol concentration in acetone is in the range of 700 to 8000 ppm by weight, and

(iv) the water content of the starting raw material for condensing is maintained to be less than 0.4% by weight (see Claim 8).

Applicants submit that none of US 4,308,404, US 4,391,997, or US 4,400,555, US 5,780,690 and JP 10-175898, even when viewed in conjunction with US 5,777,180, disclose or suggest the present invention as claimed.

In order for a reference to anticipate an invention, the reference “must teach every element of the claim” (MPEP §2131). The Examiner previously disregarded this distinction asserting “the claims read on a modification of 10 to less than 20 mol% with a methanol concentration below 250 ppm.” To clarify the claimed invention, Applicants have amended Claim 8 to specifically define four elements, must notably: “(ii) said ion exchange resin has a modification rate in the range of 26 to 65 mol%, (iii) the methanol concentration in acetone is in the range of 700 to 8000 ppm by weight.” Applicants note that at no point do US 4,308,404, US 4,391,997, or US 4,400,555, disclose or suggest the specific combination of the disclosed “ion exchange resin having a modification rate in the range of 20 to 65 mol%” and the “methanol concentration in acetone being in the range of 700 to 8000 ppm by weight.” Therefore, US 4,308,404, US 4,391,997, and US 4,400,555 fail to meet the standard for anticipation. As such the anticipation rejection is no longer tenable.

Moreover, “to establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation... to modify the reference... Second, there must be a reasonable expectation of success. Finally, the prior art reference... must teach or suggest all the claim limitations.” (MPEP §2142) In the present case, Applicants note that the art of record is silent with respect to the aforementioned elements of the claim and provides no suggestion or motivation to arrive at the same, much less an expectation of

the results flowing therefrom. To this end, Applicants direct the Examiner's attention to Examples 3 and 4 as compared to Comparative Examples 2 and 3 (*infra*).

In view of the foregoing, Applicants request withdrawal of these grounds of rejection.

The rejection of Claims 8-17 under 35 U.S.C. §103(a) over JP 10-251179 optionally in view of US 5,780,690, US 4,391,997, and US 4,400,555, is obviated by amendment.

As stated above, a critical difference between presently pending Claim 8 and the art of record is the specifically claimed combination of "(ii) said ion exchange resin has a modification rate in the range of 26 to 65 mol%" and "(iii) the methanol concentration in acetone is in the range of 700 to 8000 ppm by weight." As stated above, US 5,780,690, US 4,391,997, and US 4,400,555 fail to disclose or suggest such a limitation or the benefits flowing therefrom. Moreover, the primary reference JP 10-251179 also fails to disclose or suggest the specific combination as claimed.

As recognized by the Examiner, US 4,391,997 and US 4,400,555 do not disclose the methanol content in acetone. Applicants further note that ion exchange resins employed therein have a modification rate of about 10 mol% (see Examples). Although US 5,777,180 (cited by the Examiner as allegedly evidencing that the amount of methanol would be inherent in the prior art acetone feeds) disclose a methanol content in acetone may be about 200 ppm, none of the art of record disclose the use of acetone containing a high amount of methanol.

In fact, JP 10-251179 discloses a methanol content of 1 wt%, which equates to 10,000 ppm. This concentration exceeds that of the presently claimed invention. The Examiner asserts that "the use of 10,000 ppm of methanol does not distinguish the claims from the prior

art... the examples are not considered to be representative of the prior art nor are they commensurate in scope with the claims.” Applicants disagree with this assertion by the Examiner noting that as shown in Table 1-1, they have prepared samples ranging above, below, and within the claimed scope of the modification rate and the methanol concentration. Thus, the full scope of the claimed invention is covered in this Table 1-1 and it is thus commensurate in scope with the present invention.

Further, Example 1 of JP 10-251179 is adequately represented by Comparative Example 2 of the present invention. In Example 1 of JP 10-251179, bisphenol A is produced using an ion exchange resin having a modification rate of 30 mol% and acetone containing 1 wt% (10,000ppm) methanol, which is in vast excess of the claimed range. The Examiner’s attention is directed to Comparative Example 2 of the present invention, which approximates Example 1 of JP 10-251179. In Comparative Example 2 of the present invention, bisphenol A is produced using an ion exchange resin having a modification rate of 25 mol% and acetone containing 10,000ppm methanol. As evidenced by Table 1-2 (reproduced below), the conversion of phenol in Comparative Example 2 is significantly reduced as compared to the Examples within the scope of the present invention (see for example Examples 3-6).

Table 1-2

Conversion of Phenol (%)

	<u>First Stage Reaction</u>			<u>Second Stage Reaction</u>		
	Start of Reaction	after 300Hrs	after 600Hrs	Start of Reaction	after 300Hrs	after 300Hrs
Example 1	12. 2	10. 8	8. 7	15. 5	13. 7	11. 2
Example 2	12. 5	11. 2	9. 9	15. 6	14. 2	13. 3
Example 3	12. 1	10. 9	9. 4	15. 2	13. 8	13. 1

Example 4	10. 9	8. 2	7. 1	14. 5	12. 5	11. 8
Comp'tive Example 1	12. 3	6. 2	4. 1	15. 6	8. 1	6. 3
Comp'tive Example 2	12. 3	6. 0	3. 7	15. 4	8. 3	4. 3
Comp'tive Example 3	12. 0	7. 2	3. 4	15. 0	10. 9	5. 2
Comp'tive Example 4	10. 6	6. 2	3. 9	14. 1	11. 0	6. 1
Example 5	11. 5	10. 7	9. 5	14. 9	13. 7	13. 0
Example 6	10. 5	8. 0	6. 9	13. 7	11. 8	11. 1

The Examiner alleges, “it is clear from the teaching of the prior art that the amount of modification can be optimized for a particular methanol concentration. However, the Examiner offers no support for such an allegation. When an Examiner maintains that there is an implicit teaching or suggestion in the prior art, “the Examiner should indicate where (page and line or figure) such a teaching or suggestion appears in the prior art.” *Ex parte Jones*, 62 USPQ2d 1206, 1208 (Bd. Pat. App. & Inter. 2001) (**copy enclosed**). Therefore, the Office has not met the burden necessary to establish a *prima facie* case of obviousness.

Additionally, neither JP 10-251179, nor any of US 5,780,690, US 4,391,997, and US 4,400,555 disclose or suggest that modification rate and/or methanol concentration is a result-effective variable with regard to bisphenol A production. Thus, the present claims are patentable under the rationale of *In re Antonie*, 195 USPQ 6, 8-9 (CCPA 1977) (**copy enclosed**) (exceptions to rule that optimization of a result-effective variable is obvious, such as where the results of optimizing the variable are unexpectedly good or where the variable was not recognized to be result effective).

At best, the Examiner has set forth a basis that it may have been “obvious to try” based on the disclosures of JP 10-251179, US 5,780,690, US 4,391,997, and US 4,400,555.

However, "Obvious to try" has long been held not to constitute obviousness. *In re O'Farrell*, 7 USPQ2d 1673, 1680-81 (Fed. Cir. 1988) (**copy enclosed**). A general incentive does not make obvious a particular result, nor does the existence of techniques by which those efforts can be carried out. *In re Deuel*, 34 USPQ2d 1210, 1216 (Fed. Cir. 1995) (**copy enclosed**).

In view of the foregoing, JP 10-251179 in combination with US 5,780,690, US 4,391,997, and US 4,400,555 fail to even support a *prima facie* case of obviousness (see MPEP 2142).

Applicants request withdrawal of this ground of rejection.

Applicants respectfully traverses the obviousness-type double patenting rejections of Claims 8-17 over Claims 1-13 of US 6,740,784 and of Claims 8-17 over co-pending U.S. Application No. 10/433,155 in view of US 4,400,555.

Applicants submit that the claims of US 6,740,784 and co-pending U.S. Application No. 10/433,155 are silent with respect to the presently claimed concentration of water in the starting materials. Accordingly, Applicants submit that the presently claimed invention is not obvious in view thereof.

Withdrawal of these grounds of rejection is requested.

Application Serial No. 10/822,703
Response to Office Action mailed February 9, 2005

Applicants submit that the present application is in condition for allowance. Early notification to this effect is respectfully requested.

Respectfully submitted,

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FULL TEXT OF CASES (USPQ2D)
All Other Cases



(Unpublished) Ex parte Jones, 62 USPQ2d 1206 (BdPatApp&Int 2001)

(Unpublished)
62 USPQ2D 1206
Ex parte Jones

U.S. Patent and Trademark Office, Board of Patent Appeals and Interferences

Appeal No. 2001-1839
Decided November 28, 2001

Unpublished Opinion

(Non-precedential)

Headnotes

PATENTS

[1] Patentability/Validity — Obviousness — Combining references (§115.0905)

“Motivation” to combine teachings of prior art is not always required to support obviousness rejection under 35 U.S.C. §103, since legally sufficient rationale for finding of obviousness may be supported by reason or suggestion in prior art, as well as motivation, to

combine teachings.

[2] Practice and procedure in Patent and Trademark Office —Board of Patent Appeals and Interferences — Rules and rules practice (§110.1105)

Patentability/Validity — Obviousness — Relevant prior art — In general (§115.0903.01)

Patent examiner's citation of abstract in support of rejection without citation and reliance on underlying scientific article is generally inappropriate if both abstract and underlying document are prior art, and proper examination therefore should be based on underlying documents and translations, if necessary, since abstracts often are not written by author of underlying document, and may be erroneous; in present case, in which neither examiner nor applicant relies on underlying articles, Board of Patent Appeals and Interferences, in exercise of its discretion, will not obtain translations of underlying journal articles in order to evaluate merits of translations in first instance, since it is examiner's responsibility to obtain translations, and since review of translations by examiner and applicant may supply additional evidence as to whether there is legally sufficient reason, suggestion, teaching, or motivation to combine teachings of cited articles, and thus may eliminate need for appeal.

Case History and Disposition

Patent application of Jones, serial no. 08/947,428.1 Applicant appeals from examiner's rejection of claims 38 and 39 in application. Vacated and remanded.

[Editor's Note: The Board of Patent Appeals and Interferences has indicated that this opinion is not binding precedent of the board.]

Judge:

Before Winters and William F. Smith, administrative patent judges, and McKelvey, senior administrative patent judge.

Footnotes

1 Application for patent filed 8 October 1997.

Opinion Text

Opinion By:

McKelvey, S.J.

***Decision on appeal under
35 U.S.C. § 134***

[The text of the opinion follows.] The appeal is from a decision of a primary examiner rejecting claims 38-39. We vacate and

remand for action not inconsistent with views expressed herein.

A. Findings of fact

[Unpublished] The record supports the following findings by at least a preponderance of the evidence.²

[Unpublished] 1. The claimed invention relates to a method of making organic chemicals.

[Unpublished] 2. The examiner has rejected claims 38-39 as being unpatentable under 35 U.S.C. §103(a) over

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[Unpublished] a) Horner,

[Unpublished] b) Suri,

[Unpublished] c) Endel'man,

[Unpublished] d) Manthey and

[Unpublished] e) Ota.

[Unpublished] 3. Horner is a 25-page technical journal article written in German.

[Unpublished] 4. The examiner has placed in the record a short English-language abstract of Horner.

[Unpublished] 5. The record does not contain an English-language translation of Horner.

[Unpublished] 6. Suri is a 2-page technical journal article written in English.

[Unpublished] 7. Endel'man is a 4-page technical journal article written in Russian.

[Unpublished] 8. The examiner has placed in the record a short English-language abstract of Endel'man.

[Unpublished] 9. The record does not contain an English-language translation of Endel'man.

[Unpublished] 10. Manthey is a 5-page technical journal article written in English.

[Unpublished] 11. Ota appears to be a 5-page technical journal article written in Japanese.

[Unpublished] 12. The examiner has placed in the record a short English-language abstract of Ota.

[Unpublished] 13. The record does not contain an English-language translation of Ota.

[Unpublished] 14. The examiner does not maintain that any one of the five prior art references fully describes the claimed invention. Hence, a rejection based on 35 U.S.C. §103(a).

[Unpublished] 15. According to the examiner, “the skilled artisan looking for an alternative route for the preparation” of the product produced by the claimed method “was deemed to be aware of all the various methods of the preparation” of the product (Examiner's Answer, page 4).

[Unpublished] 16. Further according to the examiner, “one of ordinary skill in the art would be motivated [sic—would have been motivated] to prepare *** [the compound made by applicant's claimed method] by coupling

Suri's *** acid and Endel'man's *** acid as taught by Manthey followed by *** [further treatment] to yield *** [a compound] as taught by Horner and subsequent reduction as taught by Ota to arrive at the *** [claimed process]”(Examiner's Answer, pages 4-5).

[Unpublished] 17. According to applicant, the requisite “motivation” is not present in the prior art because “[t]hroughout the prosecution the examiner has failed to point out any teaching or suggestion in the prior art that would motivate the skilled artisan” to use the claimed process invention (Appeal Brief, page 4).

B. Discussion

1. Rationale in support of obviousness

[Unpublished] [1] The applicant and the examiner have apparently assumed that there always must be “motivation” to combine teachings of the prior art to support a rejection based on §103(a). The assumption is not correct. The word “motivation” or a word similar to “motivation” does not appear in 35 U.S.C. § 103(a). While a finding of “motivation” supported by substantial evidence probably will support combining teachings of different prior art references to establish a *prima facie* obviousness case, it is not always necessary. For example, where a claimed apparatus requiring Phillips head screws differs from a prior art apparatus describing the use of flathead screws, it might be hard to find motivation to substitute flathead screws with Phillips head screws to arrive at the claimed invention. However, the prior art would make it more than clear that Phillips head screws and flathead screws are viable alternatives serving the same purpose. Hence, the prior art would “suggest” substitution of flathead screws for Phillips head screws albeit the prior art might not “motivate” use of Phillips head screws in place of flathead screws.

[Unpublished] What must be established to sustain an obviousness rejection is a legally sufficient rationale as to why the claimed subject matter, as a whole, would have been obvious notwithstanding a difference between claimed subject matter and a reference which is prior art under 35 U.S.C. § 102. Once a difference is found to exist, then the examiner must articulate a legally sufficient rationale in support of a §103(a) rejection. The legally sufficient rationale may be supported by a reason, suggestion, teaching or motivation in the prior art which would have rendered obvious the claimed subject within the meaning of § 103(a). *In re Dance*, 160 F.3d 1339, 1343, 48 USPQ2d 1635, 1637 (Fed. Cir. 1998) (there must be some *teaching, suggestion* or *motivation* in the prior art to make the specific combination that was made by the applicant); *In re Gartside*, 203 F.3d 1305, 1319, 53 USPQ2d 1769, 1778 (Fed. Cir. 2000) (the best defense against the subtle but powerful attraction of a hindsight-based obviousness analysis is rigorous application of the requirement for a *teaching* or *motivation* to combine prior art references); *Pro-Mold and Tool Co. v. Great Lakes Plastics Inc.*

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, 75 F.3d 1568, 1573, 37 USPQ2d 1626, 1629 (Fed. Cir. 1996) (“there must be a *reason, suggestion, or motivation* *** to combine [the teachings of] *** references ***”); *Smiths Industries Medical Systems, Inc. v. Vital Signs, Inc.*, 183 F.3d 1347, 1356, 51 USPQ2d 1415, 1420-21 (Fed. Cir. 1999) (there is no basis for concluding that an invention would have been obvious solely because it is a combination of elements that were known in the art at the time of the invention; the relevant inquiry is whether there is a *reason, suggestion, or motivation* in the prior art that would lead one of ordinary skill in the art to combine the teachings of the references).

[Unpublished] Moreover, when an examiner maintains that there is an explicit or implicit teaching or suggestion in the prior art, the examiner should indicate where (page and line or figure) such a teaching or suggestion appears in the prior art. *In re Rijckaert*, 9 F.3d 1531, 1533, 28 USPQ2d 1955, 1957 (Fed. Cir. 1993), citing *In re Yates*, 663 F.2d 1054, 1057, 211 USPQ 1149, 1151 (CCPA 1981).

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One difficulty with the rationale in support of the examiner's rejection in this case, and for that matter the applicant's challenge to the rejection, is that it appears to be based solely on a motivation rationale without taking into account whether there otherwise is a legally sufficient *reason, showing, suggestion or teaching* which might also suffice to support the examiner's rejection. Moreover, a suggestion, teaching or motivation to combine teachings of the prior art may flow from the prior art references themselves, the knowledge of one of ordinary skill in the art, or, in some cases, from the nature of the problem to be solved. *In re Dembiczak*, 175 F.3d 994, 999, 50 USPQ2d 1614, 1617 (Fed. Cir. 1999). *See also In re Gartside, supra* at 1319, 53 USPQ2d at 1778 (the suggestions may come from, *inter alia*, the teachings of the references themselves and, in some cases, from the nature of the problem to be solved).

If the examiner determines that it is appropriate to enter a further rejection, the examiner may wish to consider a rationale based on a suggestion, teaching or other reason in place of a rationale based exclusively on motivation.

We will also note that the examiner's theory of rejection, at least in part, seems to rely on the proposition that *if* a person of ordinary skill in the art is looking for an alternative method for the preparation of a compound, then that person would be aware of all analogous art (*see* Finding 15). If the examiner continues to rely on that theory, then the examiner would be under a burden to establish why a person of ordinary skill in the art would be looking for an alternative method, particularly where a method is known for making a particular compound.

2. Use of abstracts in place of underlying articles

The principal difficulty with the prosecution of the application on appeal is the examiner's attempt to establish "motivation" by reliance on three English-language abstracts of journal articles written in foreign languages. The examiner does not maintain that only Suri and Manthey, both in English, support the rejection. The use of abstracts, when the underlying document is prior art, gives us considerable pause.

The Board of Patent Appeals and Interferences continues to have recurring problems in resolving *ex parte* appeals which come before it. One continuing recurring problem is the citation and reliance by examiners on abstracts, without citation and reliance on the underlying scientific document.

[2] In this appeal, the examiner relied upon abstracts of three technical journal articles without referring to translations of the underlying documents. Citation of an abstract without citation and reliance on the underlying scientific document itself is generally inappropriate where both the abstract and the underlying document are prior art. Abstracts often are not written by the author of the underlying document and may be erroneous. It is our opinion that a proper examination under 37 CFR § 1.104 should be based on the underlying documents and translations, where needed. Accordingly, the preferred practice is for the examiner to cite and rely on the underlying document.

When an examiner cites and relies only on an abstract, the applicant may wish to obtain a copy of the underlying document and submit a copy to the examiner when responding to a rejection relying on an abstract. In the event a reference is in a foreign language, if the applicant does not wish to expend resources to obtain a translation, the applicant may wish to request the examiner to supply a translation. If

a translation is not supplied by the examiner, the applicant may wish to consider seeking supervisory relief by way of a petition (37 CFR § 1.181) to have the examiner directed to obtain and supply a translation.

~~Unpublished~~ In the past, when neither the examiner nor the applicant relies on the underlying article, the board often expended the resources necessary to obtain a copy of the underlying scientific article, as well as translations thereof. When it did so, however, the burden of examining the application fell on the board in the first instance. Moreover, to the extent that the board relies on parts of a translation not previously provided to an applicant, any affirmance generally has to be a new ground of rejection under 37 CFR § 1.196(b)—which can result in further prosecution.

~~Unpublished~~ In this case, we do not know whether the examiner or the applicant had or reviewed the underlying foreign language technical journal articles or translations thereof. The board cannot examine, in the first instance, all applications which come before it in an *ex parte* appeal under 35 U.S.C. § 134. In this particular appeal, we exercise discretion by declining to obtain translations of the underlying technical journal articles and thereafter evaluate on the merits in the first instance the translations. In our view, obtaining translations is the responsibility of the examiner. A review by the examiner and applicant of translations of the prior art relied upon in support of the examiner's rejection may supply additional relevant evidence as to whether there is a legally sufficient reason, suggestion, teaching or motivation to combine the teachings of the five technical journal articles. Moreover, an evaluation of translations may eliminate the need for an appeal.

C. Decision

~~Unpublished~~ The decision of the examiner rejecting claims 38-39 under 35 U.S.C. § 103(a) over (1) Horner, (2) Suri, (3) Endel'man, (4) Manthey and (5) Ota is *vacated* and the application is *remanded* to the examiner. For the effect of a decision vacating an examiner's rejection, see *In re Zambrano*, 58 USPQ2d 1312 (Bd. Pat. App. & Int. 2001) (explaining that vacated rejection no longer exists).

~~Unpublished~~ The examiner and/or the applicant may obtain translations of (A) Horner, (B) Endel'man and (C) Ota.

~~Unpublished~~ Nothing in this opinion should be read as precluding the examiner from entering a rejection based on translations. In the event the examiner determines that claims 38-39 are unpatentable over the combination of the five references (or any additional prior art), then the examiner must identify and cite the specific portions (page and line or figure) of each article or prior art document upon which he relies in support of any rejection. We are primarily a board of review. Accordingly, neither the examiner nor applicant should expect in any further appeal for us to dig through five prior art references to come up with a theory which might support or negate a rejection in the first instance. Moreover, if the examiner enters a further rejection based on foreign language document, translations must be obtained if a further appeal is taken. We will not decide a further appeal without translations.

We express no views on the ultimate merits of any rejection under 35 U.S.C. § 103(a) based on the five prior art references or any additional prior art which the examiner and applicant may wish to make of record.

D. Order

~~Unpublished~~ Upon consideration of the appeal, and for the reasons given, it is

~~Unpublished~~ ORDERED that the examiner's rejection under §103(a) of claims 38-39 is *vacated*.

~~Unpublished~~ FURTHER ORDERED that the application is *remanded* to the examiner for action not inconsistent with the views expressed in this opinion.

~~Unpublished~~ FURTHER ORDERED that no time period for taking any subsequent action in connection with this appeal may be extended under 37 CFR § 1.136(a).

VACATED and REMANDED

Footnotes

2 To the extent these findings of fact discuss legal issues, they may be treated as conclusions of law.

- End of Case -



FULL TEXT OF CASES (USPQ2D)
All Other Cases

In re O'Farrell (CA FC) 7 USPQ2d 1673 In re O'Farrell

**U.S. Court of Appeals Federal Circuit
7 USPQ2d 1673**

**Decided August 10, 1988
No. 87-1486**

Headnotes

PATENTS

1. Patentability/Validity -- Obviousness -- Evidence of (§ 115.0906)

Applicants' method of producing predetermined protein in stable form in host species of bacteria through genetic engineering is obvious within meaning of 35 USC 103 since reference, authored by two of three patent applicants and published more than one year prior to patent application date, contained detailed enabling methodology for practicing claimed invention, suggestion for modifying prior art to practice claimed invention, and evidence suggesting that invention could be successful, and reference thus rendered invention obvious to those of ordinary skill in art at time invention was made.

2. Patentability/Validity -- Obviousness -- Evidence of (§ 115.0906)

Experimenters' use of heterologous gene coded for ribosomal RNA, which is not ordinarily translated, rather than gene coded for predetermined protein, in plasmid cloning vector for introduction into host bacteria in genetic engineering experiment, does not require finding that applicant's claimed method of producing predetermined protein in host bacteria through genetic engineering was not obvious in view of published paper describing experiment, particularly observation that hybrid messenger RNA produced by experiment was apparently translated into protein, since it would have been obvious and reasonable to conclude from such observation that if gene coded for ribosomal RNA produced "junk" or "nonsense" protein, then use of gene coded for predetermined protein would

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result in production of "useful" protein, as application claims.

3. Patentability/Validity -- Obviousness -- In general (§ 115.0901)

Rejection of patent application cannot be overturned on ground that examiner and Board of Patent Appeals and Interferences applied impermissible "obvious to try" standard, since assignment of error for application of such standard usually occurs when invention is made by varying all parameters or trying each of numerous choices until successful without indication in prior art as to which parameters were critical or which choices were likely to be successful, or when invention is made by exploring promising new technology or general approach with only general guidance from prior art as to particular form of claimed invention or how to achieve it, and since neither situation is present in instant case.

4. Patentability/Validity -- Obviousness -- In general (§ 115.0901)

Finding of obviousness under 35 USC 103 requires only that prior art reveal reasonable expectation of success in producing claimed invention, rather than absolute prediction of such success.

Case History and Disposition:

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Appeal from decision of Patent and Trademark Office, Board of Patent Appeals and Interferences.

Patent application, serial no. 180,424, filed by Patrick H. O'Farrell, Barry O. Polisky, and David H. Gelfand. From decision of Board of Patent Appeals and Interferences affirming final rejection of application on grounds of obviousness, applicants appeal. Affirmed.

Attorneys:

J. Bruce McCubbrey of Fitch, Even, Tabin & Flannery (Virginia H. Meyer, with them on brief), San Francisco, Calif., for appellant.

Harris A. Pitlick, associate solicitor, Patent and Trademark Office (Joseph F. Nakamura, solicitor and Fred E. McKelvey, deputy solicitor, with him on brief), for appellee.

Judge:

Before Markey, chief judge, and Rich and Nies, circuit judges.

Opinion Text

Opinion By:
Rich, J.

This appeal is from the decision of the United States Patent and Trademark Office Board of Patent Appeals and Interferences (board) affirming the patent examiner's final rejection of patent application Serial No. 180,424, entitled "Method and Hybrid Vector for Regulating Translation of heterologous DNA in Bacteria." The application was rejected under 35 USC 103 on the ground that the claimed invention would have been obvious at the time the invention was made in view of a published paper by two of the three coinventors, and a publication by Bahl, Mariani & Wu 1 *Gene* 81 (1976) (Bahl). We affirm.

The claimed invention is from the developing new field of genetic engineering. A broad claim on appeal reads:

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Claim 1. A method for producing a predetermined protein in a stable form in a transformed host species of bacteria comprising, providing a cloning vector which includes at least a substantial portion of a gene which is indigenous to the host species of bacteria and is functionally transcribed and translated in that species, said substantial portion of said indigenous gene further including the regulatory DNA sequences for RNA synthesis and protein synthesis but lacking the normal gene termination signal, and linking a natural or synthetic heterologous gene encoding said predetermined protein to said indigenous gene portion at its distal end, said heterologous gene being in proper orientation and having codons arranged in the same reading frame as the codons of said indigenous gene so that readthrough can occur from said indigenous gene portion into said heterologous gene in the same reading frame, said heterologous gene portion further containing sufficient DNA sequences to result in expression of a fused protein having sufficient size so as to confer stability on said predetermined protein when said vector is used to transform said host species of bacteria.

Illustrative embodiments are defined in more specific claims. For example:

Claim 2. A method for producing a predetermined protein in a stable form in a transformed host species of bacteria, comprising, providing an *E. coli* plasmid having an operator, a promoter, a site for the initiation of translation, and at least a substantial portion of the beta-galactosidase gene of the *E. coli* lactose operon, said substantial portion of said beta-galactosidase gene being under the control of said operator, promoter and site for initiation of translation, said substantial portion of said beta-galactosidase gene lacking the normal gene termination signal, and linking a heterologous gene encoding said predetermined protein to said beta-galactosidase gene portion at its distal end, said heterologous gene being in proper orientation and having codons arranged in the same reading frame as the codons of the said beta-galactosidase gene portion so that readthrough can occur from said beta-galactosidase gene portion into said heterologous gene in the same reading frame, said heterologous gene portion further containing sufficient DNA sequences to result in expression of a fused protein having sufficient size so as to confer stability on said predetermined protein when said vector is used to transform said host species of bacteria.

Claim 3. The method of Claim 2 wherein said *E. coli* plasmid comprises the plasmid designated pBGP120.

Although the terms in these claims would be familiar to those of ordinary skill in genetic engineering, they employ a bewildering vocabulary new to those who are not versed in molecular biology. An understanding of the science and technology on which these claims are based is essential before one can analyze and explain whether the claimed invention would have been obvious in light of the prior art.

I. Background 1

Proteins are biological molecules of enormous importance. Proteins include enzymes that catalyze biochemical

reactions, major structural materials of the animal body, and many hormones. Numerous patents and applications for patents in the field of biotechnology involve specific proteins or methods for making and using proteins. Many valuable proteins occur in nature only in minute quantities, or are difficult to purify from natural sources. Therefore, a goal of many biotechnology projects, including appellants' claimed invention, is to devise methods to synthesize useful quantities of specific proteins by controlling the mechanism by which living cells make proteins.

The basic organization of all proteins is the same. Proteins are large polymeric molecules consisting of chains of smaller building blocks, called *amino acids*, that are linked together covalently. 2 The chemical bonds linking amino acids together are called *peptide* bonds, so proteins are also called *poly*

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peptides. 3 It is the exact sequence in which the amino acids are strung together in a polypeptide chain that determines the identity of a protein and its chemical characteristics. 4 Although there are only 20 amino acids, they are strung together in different orders to produce the hundreds of thousands of proteins found in nature.

To make a protein molecule, a cell needs information about the sequence in which the amino acids must be assembled. The cell uses a long polymeric molecule, DNA (deoxyribonucleic acid), to store this information. The subunits of the DNA chain are called *nucleotides*. A nucleotide consists of a nitrogen-containing ring compound (called a *base*) linked to a 5-carbon sugar that has a phosphate group attached. 5 DNA is composed of only four nucleotides. They differ from each other in the base region of the molecule. The four bases of these subunits are adenine, guanine, cytosine, and thymine (abbreviated respectively as A, G, C and T). The sequence of these bases along the DNA molecule specifies which amino acids will be inserted in sequence into the polypeptide chain of a protein.

DNA molecules do not participate directly in the synthesis of proteins. DNA acts as a permanent "blueprint" of all of the genetic information in the cell, and exists mainly in extremely long strands (called *chromosomes*) containing information coding for the sequences of many proteins, most of which are not being synthesized at any particular moment. The region of DNA on the chromosome that codes for the sequence of a single polypeptide is called a *gene*, 6 In order to *express* a gene (the process whereby the information in a gene is used to synthesize new protein), a copy of the gene is first made as a molecule of RNA (ribonucleic acid).

RNA is a molecule that closely resembles DNA. It differs, however in that it contains a different sugar (ribose instead of deoxyribose) and the base thymine (T) of DNA is replaced in RNA by the structurally similar base, uracil (U). Making an RNA copy of DNA is called *transcription*. The transcribed RNA copy contains sequences of A, U, C, and G that carry the same information as the sequence of A, T, C, and G in the DNA. That RNA molecule, called *messenger RNA*, then moves to a location in the cell where proteins are synthesized.

The code whereby a sequence of nucleotides along an RNA molecule is translated into a sequence of amino acids in a protein (i.e., the "genetic code") is based on serially reading groups of three adjacent nucleotides. Each combination of three adjacent nucleotides, called a *codon*, specifies a particular amino acid. For example, the codon U-G-G in a messenger RNA molecule specifies that there will be a tryptophan molecule in the corresponding location in the corresponding polypeptide. The four bases A, G, C and U can be combined as triplets in 64 different ways, but there are only 20 amino acids to be coded. Thus, most amino acids are coded for by more than one codon. For example, both U-A-U and U-A-C code for tyrosine, and there are six different codons that code for leucine. There are also three codons that do not code for any amino acid (namely, U-A-A, U-G-A, and U-A-G). Like periods at the end of a sentence, these sequences signal the end of the polypeptide chain, and they are therefore called *stop codons*.

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The cellular machinery involved in synthesizing proteins is quite complicated, and centers around large structures called *ribosomes* that bind to the messenger RNA. The ribosomes and associated molecules "read" the information in the messenger RNA molecule, literally shifting along the strand of RNA three nucleotides at a time, adding the amino acid specified by that codon to a growing polypeptide chain that is also attached to the ribosome. When a stop codon is reached, the polypeptide chain is complete and detaches from the ribosome.

The conversion of the information from a sequence of codons in an RNA molecule into the sequence of amino acids in a newly synthesized polypeptide is called *translation*. A messenger RNA molecule is typically reused to make many copies of the same protein. Synthesis of a protein is usually terminated by destroying the messenger RNA. (The information for making more of that protein remains stored in DNA in the chromosomes.)

The translation of messenger RNA begins at a specific sequence of nucleotides that bind the RNA to the ribosome and specify which is the first codon that is to be translated. Translation then proceeds by reading nucleotides, three at a time, until a stop codon is reached. If some error were to occur that shifts the frame in which the nucleotides are read by one or two nucleotides, all of the codons after this shift would be misread. For example, the sequence of codons [. . . C-U-C-A-G-C-G-U-U-A-C-C- A. . .] codes for the chain of amino acids

[. . . leucine-serine-valine-threonine-. . .]. If the reading of these groups of three nucleotides is displaced by one nucleotide, such as [. . . C-U-C-A-G-C-G-U-U-A-C-C-A . . .], the resulting peptide chain would consist of [. . . serine-alanine-leucine-proline. . .]. This would be an entirely different peptide, and most probably an undesirable and useless one. Synthesis of a particular protein requires that the correct register or *reading frame* be maintained as the codons in the RNA are translated.

The function of messenger RNA is to carry genetic information (transcribed from DNA) to the protein synthetic machinery of a cell where its information is translated into the amino acid sequence of a protein. However, some kinds of RNA have other roles. For example, ribosomes contain several large strands of RNA that serve a structural function (*ribosomal RNA*). Chromosomes contain regions of DNA that code for the nucleotide sequences of structural RNAs and these sequences are transcribed to manufacture those RNAs. The DNA sequences coding for structural RNAs are still called genes even though the nucleotide sequence of the structural RNA is never translated into protein.

Man, other animals, plants, protozoa, and yeast are *eucaryotic* (or eukaryotic) organisms: their DNA is packaged in chromosomes in a special compartment of the cell, the nucleus. Bacteria (*procaryotic* or prokaryotic organisms) have a different organization. Their DNA, usually a circular loop, is not contained in any specialized compartment. Despite the incredible differences between them, all organisms, whether eucaryote or procaryote, whether man or mouse or lowly bacterium, use the same molecular rules to make proteins under the control of genes. In all organisms, codons in DNA are transcribed into codons in RNA which is translated on ribosomes into polypeptides according to the same genetic code. Thus, if a gene from a man is transferred into a bacterium, the bacterium can manufacture the human protein. Since most commercially valuable proteins come from man or other eucaryotes while bacteria are essentially little biochemical factories that can be grown in huge quantities, one strategy for manufacturing a desired protein (for example, insulin) is to transfer the gene coding for the protein from the eucaryotic cell where the gene normally occurs into a bacterium.

Bacteria containing genes from a foreign source (*heterologous* genes) integrated into their own genetic makeup are said to be *transformed*. When transformed bacteria grow and divide, the inserted heterologous genes, like all the other genes that are normally present in the bacterium (*indigenous* genes), are replicated and passed on to succeeding generations. One can produce large quantities of transformed bacteria that contain transplanted heterologous genes. The process of making large quantities of identical copies of a gene (or other fragment of DNA) by introducing it into procaryotic cells and then growing those cells is called *cloning* the gene. After growing sufficient quantities of the transformed bacteria, the biotechnologist must induce the transformed bacteria to *express* the cloned gene and make useful quantities of the protein. This is the purpose of the claimed invention.

In order to make a selected protein by expressing its cloned gene in bacteria, several technical hurdles must be

overcome. First the gene coding for the specific protein must be isolated for cloning. This is a formidable task, but recombinant DNA technology has armed the genetic engineer with a variety of

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techniques to accomplish it. 7 Next the isolated gene must be introduced into the host bacterium. This can be done by incorporating the gene into a cloning vector. A *cloning vector* is a piece of DNA that can be introduced into bacteria and will then replicate itself as the bacterial cells grow and divide. Bacteriophage (viruses that infect bacteria) can be used as cloning vectors, but plasmids were the type used by appellants. A *plasmid* is a small circular loop of DNA found in bacteria, separate from the chromosome, that replicates like a chromosome. It is like a tiny auxilliary chromosome containing only a few genes. Because of their small size, plasmids are convenient for the molecular biologist to isolate and work with. Recombinant DNA technology can be used to modify plasmids by splicing in cloned eucaryotic genes and other useful segments of DNA containing control sequences. Short pieces of DNA can even be designed to have desired nucleotide sequences, synthesized chemically, and spliced into the plasmid. One use of such chemically synthesized linkers is to insure that the inserted gene has the same reading frame as the rest of the plasmid; this is a teaching of the Bahl reference cited against appellants. A plasmid constructed by the molecular geneticist can be inserted into bacteria, where it replicates as the bacteria grow. Even after a cloned heterologous gene has been successfully inserted into bacteria using a plasmid as a cloning vector, and replicates as the bacteria grow, there is no guarantee that the gene will be expressed, i.e., transcribed and translated into protein. A bacterium such as *E. coli* (the species of bacterium used by appellants) has genes for several thousand proteins. At any given moment many of those genes are not expressed at all. The genetic engineer needs a method to "turn on" the cloned gene and force it to be expressed. This is the problem appellants worked to solve.

II. Prior art

Appellants sought to control the expression of cloned heterologous genes inserted into bacteria. They reported the results of their early efforts in a publication, the three authors of which included two of the three coinventor-appellants (the Polisky reference 8), that is undisputed prior art against them. Their strategy was to link the foreign gene to a highly regulated indigenous gene. Turning on expression of the indigenous gene by normal control mechanisms of the host would cause expression of the linked heterologous gene.

As a controllable indigenous gene, the researchers chose a gene in the bacterium *E. coli* that makes beta-galactosidase. *Beta-galactosidase* is an enzyme needed to digest the sugar, lactose (milk sugar). When *E. coli* grows in a medium that contains no lactose, it does not make beta-galactosidase. If lactose is added to the medium, the gene coding for beta galactosidase is expressed. The bacterial cell makes beta-galactosidase and is then able to use lactose as a food source. When lactose is no longer available, the cell again stops expressing the gene for beta galactosidase.

The molecular mechanisms through which the presence of lactose turns on expression of the beta-galactosidase gene has been studied in detail, and is one of the best understood examples of how gene expression is regulated on the molecular level. The beta-galactosidase gene is controlled by segments of DNA adjacent to the gene. These *regulatory DNA sequences* (the general term used in Claim 1) include the *operator* and *promoter* sequences (specified in Claim 2). 9 The researchers constructed a plasmid containing the beta-galactosidase gene with its operator and promoter. This gene (with its regulatory sequences) was removed from the chromosome of *E. coli* where it is normally found and was transplanted to a plasmid that could be conveniently manipulated.

Restriction endonucleases are useful tools in genetic engineering. These enzymes cut strands of DNA, but only at places where a specific sequence of nucleotides is present. For example, one restriction endonuclease, called *EcoRI*, cuts DNA only at sites where

the nucleotide sequence is [. . .G-A-A-T-T-C-. . .]. With restriction enzymes the genetic engineer can cut a strand of DNA at very specific sites into just a few pieces. With the help of "repair" enzymes, other pieces of DNA can be spliced onto the cut ends. The investigators found that the plasmid which they had constructed contained only two sequences that were cut by EcoRI. They were able to eliminate one of these sites that was unwanted. They were then left with a plasmid containing the beta-galactosidase gene with its regulatory sequences, and a single EcoRI site that was within the beta-galactosidase gene and close to its stop codon. They named this plasmid that they had constructed pBGP120.

The next step was to cut the plasmid open at its EcoRI site and insert a heterologous gene from another organism. The particular heterologous gene they chose to splice in was a segment of DNA from a frog that coded for ribosomal RNA. The frog gene was chosen as a test gene for reasons of convenience and availability. The new plasmid created by inserting the frog gene was similar to pBGP120, but its beta-galactosidase gene was incomplete. Some codons including the stop codon were missing from its end, which instead continued on with the sequence of the frog ribosomal RNA gene. The investigators named this new plasmid pBGP123. They inserted this plasmid back into *E. coli* and grew sufficient quantities for study. They then fed the *E. coli* with lactose. As they had intended, the lactose turned on transcription of the beta-galactosidase gene in the plasmid. RNA polymerase moved along the plasmid producing a strange new kind of RNA: Each long strand of RNA first contained codons for the messenger RNA for beta-galactosidase and then continued without interruption with the codons for the frog ribosomal RNA. Thus, there was *read-through* transcription in which the RNA polymerase first transcribed the indigenous (beta-galactosidase) gene and then "read through," i.e., continued into and through the adjacent heterologous (frog ribosomal RNA) gene. Although the RNA produced was a hybrid, it nevertheless contained a nucleotide sequence dictated by DNA from a frog. The researchers had achieved the first controlled transcription of an animal gene inside a bacterium.

The researchers had used a gene coding for a ribosomal RNA as their heterologous test gene. Ribosomal RNA is not normally translated into protein. Nevertheless, they were obviously interested in using their approach to make heterologous proteins in bacteria. They therefore examined the beta-galactosidase made by their transformed bacteria. Patrick O'Farrell, who was not a coauthor of the Polisky paper but was to become a coinventor in the patent application, joined as a collaborator. They found that beta-galactosidase from the transformed bacteria had a higher molecular weight than was normal. They concluded that the bacteria must have used their strange new hybrid RNA like any other messenger RNA and translated it into protein. When the machinery of protein synthesis reached the premature end of the sequence coding for beta-galactosidase it continued right on, three nucleotides at a time, adding whatever amino acid was coded for by those nucleotides, until a triplet was reached with the sequence of a stop codon. The resulting polypeptide chains had more amino acids than normal beta-galactosidase, and thus a higher molecular weight. The researchers published their preliminary results in the Polisky article. They wrote: if the normal translational stop signals for [beta]-galactosidase are missing in pBGP120, in-phase translational readthrough into adjacent inserted sequences might occur, resulting in a significant increase in the size of the [beta]-galactosidase polypeptide subunit. In fact, we have recently observed that induced cultures of pBGP123 contain elevated levels of [beta]-galactosidase of higher subunit molecular weight than wild-type enzyme (P. O'Farrell, unpublished experiments). We believe this increase results from translation of *Xenopus* [frog] RNA sequences covalently linked to [messenger] RNA for [beta]-galactosidase, resulting in a fused polypeptide. Polisky at 3904.

Since ribosomal RNA is never translated in normal cells, the polypeptide chain produced by translating that chain was not a naturally occurring, identified protein. The authors of the Polisky paper explicitly pointed out that if one were to insert a heterologous gene coding for a protein into their plasmid, it should produce a "fused protein" consisting of a polypeptide made of beta-galactosidase plus the protein coded for by the inserted gene, joined by a peptide bond into a single continuous polypeptide chain:

It would be interesting to examine the expression of a normally translated eukaryotic sequence in pBGP120. If an inserted sequence contains a ribosome binding site that can be utilized in bacteria, production of high levels of a readthrough transcript might allow for extensive translation of a functional eukaryotic polypeptide. In the absence of an independent ribosome bind

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ing site, the eukaryotic sequence would be translated to yield a peptide covalently linked to [beta]-galactosidase. The extent of readthrough translation under *lac* control will depend on the number of translatable codons between the EcoRI site and the first in-phase nonsense [i.e., stop] codon in the inserted sequence.

Id.

III. The Claimed Invention

Referring back to Claims 1 through 3, it can be seen that virtually everything in the claims was present in the prior art Polisky article. The main difference is that in Polisky the heterologous gene was a gene for ribosomal RNA while the claimed invention substitutes a gene coding for a predetermined protein. Ribosomal RNA gene is not normally translated into protein, so expression of the heterologous gene was studied mainly in terms of transcription into RNA. Nevertheless, Polisky mentioned preliminary evidence that the transcript of the ribosomal RNA gene was translated into protein. Polisky further predicted that if a gene that codes for a protein were to be substituted for the ribosomal RNA gene, "a readthrough transcript might allow for extensive translation of a functional eukaryotic polypeptide." Thus, the prior art explicitly suggested the substitution that is the difference between the claimed invention and the prior art, and presented preliminary evidence suggesting that the method could be used to make proteins. Appellants reduced their invention to practice some time in 1976 and reported their results in a paper that was published in 1978. 10 During 1977 they communicated their results to another group of researchers who used the readthrough translation approach to achieve the first synthesis of a human protein in bacteria. 11 Appellants filed an application to patent their invention on August 9, 1978, of which the application on appeal is a division.

IV. The Obviousness Rejection

The application was rejected under 35 USC 103. The position of the examiner and the Board is, simply, that so much of the appellant's method was revealed in the Polisky reference that making a protein by substituting its gene for the ribosomal RNA gene in Polisky (as suggested by Polisky) would have been obvious to one of ordinary skill in the art at the time that the invention was made.

The claims specify that the heterologous gene should be inserted into the plasmid in the same orientation and with the same reading frame as the preceding portion of the indigenous gene. In view of this limitation, the §103 rejection was based either on Polisky alone (supplemented by the fact that the importance of orientation and reading frame was well known in the prior art) or in combination with the Bahl reference which describes a general method for inserting a piece of chemically synthesized DNA into a plasmid. Bahl teaches that this technique could be used to shift the sequence of DNA inserted into a plasmid into the proper reading frame.

Appellants argue that at the time the Polisky article was published, there was significant unpredictability in the field of molecular biology so that the Polisky article would not have rendered the claimed method obvious to one of ordinary skill in the art. Even though there was speculation in the article that genes coding for proteins could be substituted for the ribosomal RNA gene and would be expressed as readthrough translation into the protein, this had never been done. Appellants say that it was not yet certain whether a heterologous protein could actually be produced in bacteria, and if it could, whether additional mechanisms or methods would be required. They contend

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that without such certainty the predictions in the Polisky paper, which hindsight now shows to have been correct,

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were merely invitations to those skilled in the art to try to make the claimed invention. They argue that the rejection amounts to the application of a standard of "obvious to try" to the field of molecular biology, a standard which this court and its predecessors have repeatedly rejected as improper grounds for a §103 rejection. *E.g.*, *In re Fine*, 837 F.2d 1071, 1075, 5 USPQ2d 1596, 1599 (Fed. Cir. 1988); *In re Geiger*, 815 F.2d 686, 688, 2 USPQ2d 1276, 1278 (Fed. Cir. 1987); *In re Merck & Co., Inc.*, 800 F.2d 1091, 1097, 231 USPQ 375, 379 (Fed. Cir. 1986); *In re Antonie*, 559 F.2d 618, 620, 195 USPQ 6, 8 (CCPA 1977).

Obviousness under §103 is a question of law. *Panduit Corp. v. Dennison Mfg. Co.*, 810 F.2d 1561, 1568, 1 USPQ2d 1593, 1597 (Fed. Cir.), *cert. denied*, 107 S.Ct. 2187 (1987). An analysis of obviousness must be based on several factual inquiries: (1) the scope and content of the prior art; (2) the differences between the prior art and the claims at issue; (3) the level of ordinary skill in the art at the time the invention was made; and (4) objective evidence of nonobviousness, if any. *Graham v. John Deere Co.*, 383 U.S. 1, 17-18, 148 USPQ 459, 467 (1966). *See, e.g.*, *Custom Accessories, Inc. v. Jeffrey-Allan Indus.*, 807 F.2d 955, 958, 1 USPQ2d 1196, 1197 (Fed. Cir. 1986). The scope and content of the prior art and the differences between the prior art and the claimed invention have been examined in sections II and III, *supra*. Appellants say that in 1976 those of ordinary skill in the arts of molecular biology and recombinant DNA technology were research scientists who had "extraordinary skill in relevant arts" and "were among the brightest biologists in the world." Objective evidence of nonobviousness was not argued.

[1] With the statutory factors as expounded by *Graham* in mind and considering all of the evidence, this court must determine the correctness of the board's legal determination that the claimed invention as a whole would have been obvious to a person having ordinary skill in the art at the time the invention was made. We agree with the board that appellants' claimed invention would have been obvious in light of the Polisky reference alone or in combination with Bahl within the meaning of §103. Polisky contained detailed enabling methodology for practicing the claimed invention, a suggestion to modify the prior art to practice the claimed invention, and evidence suggesting that it would be successful.

[2] Appellants argue that after the publication of Polisky, successful synthesis of protein was still uncertain. They belittle the predictive value of the observation that expression of the transcribed RNA in Polisky produced beta-galactosidase with a greater than normal molecular weight, arguing that since ribosomal RNA is not normally translated, the polypeptide chains that were added to the end of the beta-galactosidase were "junk" or "nonsense" proteins. This characterization ignores the clear implications of the reported observations. The Polisky study directly proved that a readthrough transcript messenger RNA had been produced. The preliminary observation showed that this messenger RNA was read and used for successful translation. It was well known in the art that ribosomal RNA was made of the same nucleotides as messenger RNA, that any sequence of nucleotides could be read in groups of three as codons, and that reading these codons should specify a polypeptide chain that would elongate until a stop codon was encountered. The preliminary observations thus showed that codons beyond the end of the beta-galactosidase gene were being translated into peptide chains. This would reasonably suggest to one skilled in the art that if the codons inserted beyond the end of the beta-galactosidase gene coded for a "predetermined protein," that protein would be produced. In other words, it would have been obvious and reasonable to conclude from the observation reported in Polisky that since nonsense RNA produced nonsense polypeptides, if meaningful RNA was inserted instead of ribosomal RNA, useful protein would be the result. The relative shortness of the added chains is also not a source of uncertainty, since one skilled in the art would have known that a random sequence of nucleotides would produce a stop codon before the chain got too long. 12

Appellants complain that since predetermined proteins had not yet been produced in transformed bacteria, there was uncertainty as to whether this could be done, and that the rejection is thus founded on an impermissible "obvious to try" standard. It is true that this court and its predecessors have repeatedly emphasized that "obvious to try" is not the standard under §103. However, the meaning of this maxim is sometime lost. Any invention that would in fact have been obvious under §103 would also have been, in a sense, obvious to try. The question is: when is an

invention that was obvious to try nevertheless nonobvious?

[3] The admonition that "obvious to try" is not the standard under § 103 has been directed mainly at two kinds of error. In some cases, what would have been "obvious to try" would have been to vary all parameters or try each of numerous possible choices until one possibly arrived at a successful result, where the prior art gave either no indication of which parameters were critical or no direction as to which of many possible choices is likely to be successful. *E.g.*, *In re Geiger*, 815 F.2d at 688, 2 USPQ2d at 1278; *Novo Industri A/S v. Travenol Laboratories, Inc.*, 677 F.2d 1202, 1208, 215 USPQ 412, 417 (7th Cir. 1982); *In re Yates*, 663 F.2d 1054, 1057, 211 USPQ 1149, 1151 (CCPA 1981); *In re Antonie*, 559 F.2d at 621, 195 USPQ at 8-9. In others, what was "obvious to try" was to explore a new technology or general approach that seemed to be a promising field of experimentation, where the prior art gave only general guidance as to the particular form of the claimed invention or how to achieve it. *In re Dow Chemical Co.*, 837 F.2d, 469, 473, 5 USPQ2d 1529, 1532 (Fed. Cir. 1985); *Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1380, 231 USPQ 81, 90-91 (Fed. Cir. 1986), *cert. denied*, 107 S.Ct. 1606 (1987); *In re Tomlinson*, 363 F.2d 928, 931, 150 USPQ 623, 626 (CCPA 1966). Neither of these situations applies here.

[4] Obviousness does not require absolute predictability of success. Indeed, for many inventions that seem quite obvious, there is no absolute predictability of success until the invention is reduced to practice. There is always at least a possibility of unexpected results, that would then provide an objective basis for showing that the invention, although apparently obvious, was in law nonobvious. *In re Merck & Co.*, 800 F.2d at 1098, 231 USPQ at 380; *Lindemann Maschinenfabrik GMBH v. American Hoist & Derrick Co.*, 730 F.2d 1452, 1461, 221 USPQ 481, 488 (Fed. Cir. 1984); *In re Papesch*, 315 F.2d 381, 386-87, 137 USPQ 43, 47-48 (CCPA 1963). For obviousness under §103, all that is required is a reasonable expectation of success. *In re Longi*, 759 F.2d 887, 897, 225 USPQ 645, 651-52 (Fed. Cir. 1985); *In re Clinton*, 527 F.2d 1226, 1228, 188 USPQ 365, 367 (CCPA 1976). The information in the Polisky reference, when combined with the Bahl reference provided such a reasonable expectation of success. Appellants published their pioneering studies of the expression of frog ribosomal RNA genes in bacteria more than a year before they applied for a patent. After providing virtually all of their method to the public without applying for a patent within a year, they foreclosed themselves from obtaining a patent on a method that would have been obvious from their publication to those of ordinary skill in the art, with or without the disclosures of other prior art. The decision of the board is

AFFIRMED .

Footnotes

Footnote 1. Basic background information about molecular biology and genetic engineering, can be found in Alberts, Bray, Lewis, Raff, Roberts & Watson, *The Molecular Biology of the Cell*, 1-253, 385-481 (1983) [hereinafter *The Cell*]; Watson, Hopkins, Roberts, Steitz & Weiner, *The Molecular Biology of the Gene*, Vol. 1 (4th ed., 1987) 3-502 [hereinafter *The Gene*]. These standard textbooks were used to supplement the information in the glossary supplied by appellants. The description here is necessarily simplified and omits important facts and concepts that are not necessary for the analysis of this case.

Footnote 2. There are twenty amino acids: alanine, valine, leucine, isoleucine, proline, phenylalanine, methionine, tryptophan, glycine, asparagine, glutamine, cysteine, serine, threonine, tyrosine, aspartic acid, glutamic acid, lysine, arginine, and histidine.

Footnote 3. Proteins are often loosely called *peptides*, but technically proteins are only the larger peptides with chains of at least 50 amino acids, and more typically hundreds of amino acids. Some proteins consist of several

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polypeptide chains bound together covalently or noncovalently. The term "peptide" is broader than "protein" and also includes small chains of amino acids linked by peptide bonds, some as small as two amino acids. Certain small peptides have commercial or medical significance.

Footnote 4. Polypeptide chains fold up into complex 3-dimensional shapes. It is the shape that actually determines many chemical properties of the protein. However, the configuration of a protein molecule is determined by its amino acid sequence. *The Cell* at 111-12; *The Gene* at 50-54.

Footnote 5. The sugar in DNA is deoxyribose, while the sugar in RNA, *infra*, is ribose. The sugar and phosphate groups are linked covalently to those of adjacent nucleotides to form the backbone of the long unbranched DNA molecule. The bases project from the chain, and serve as the "alphabet" of the genetic code.

DNA molecules actually consist of two chains tightly entwined as a double helix. The chains are not identical but instead are complementary: each A on one chain is paired with a T on the other chain, and each C has a corresponding G. The chains are held together by noncovalent bonds between these complementary bases. This double helical structure plays an essential role in the replication of DNA and the transmission of genetic information. *See generally The Cell* at 98-106; *The Gene* at 65-79. However, the information of only one strand is used for directing protein synthesis, and it is not necessary to discuss the implication of the double-stranded structure of DNA here. RNA molecules, *infra*, are single stranded.

Footnote 6. Chromosomes also contain regions of DNA that are not part of genes, i.e., do not code for the sequence of amino acids in proteins. These include sections of DNA adjacent to genes that are involved in the control of transcription, *infra*, and regions of unknown function.

Footnote 7. *See The Cell* at 185-194; *The Gene* at 208-10.

Footnote 8. Polisky, Bishop & Gelfand, *A plasmid cloning vehicle allowing regulated expression of eukaryotic DNA in bacteria*, 73 Proc. Nat'l Acad. Sci. USA 3900 (1976).

Footnote 9. The *promoter* is a sequence of nucleotides where the enzyme that synthesizes RNA, *RNA polymerase*, attaches to the DNA to start the transcription of the beta-galactosidase gene. The *operator* is an overlapping DNA sequence that binds a small protein present in the cell, the lactose repressor protein. The lactose repressor protein binds to the operator and physically blocks the RNA polymerase from properly attaching to the promoter so that transcription cannot proceed. Lactose molecules interact with the lactose repressor protein and cause it to change its shape; after this change in shape it moves out of the way and no longer prevents the RNA polymerase from binding to the promoter. Messenger RNA coding for beta-galactosidase can then be transcribed. *See generally The Cell* at 438-39; *The Gene* at 474-80.

Footnote 10. O'Farrell, Polisk & Gelfand, *Regulated expression by readthrough translation from a plasmid-encoded beta-galactosidase*, 134 J. Bacteriol. 645 (1978). The heterologous genes expressed in these studies were not predetermined, but were instead unidentified genes of unknown origin. The authors speculated that they were probably genes from *E. coli* that were contaminants in the source of beta-galactosidase genes. *Id.* at 648

Footnote 11. Itakura, Hirose, Crea, Riggs, Heynecker, Bolivar & Boyer, *Expression in Escherichia coli of a chemically synthesized gene for the hormone somatostatin*, 198 Science 1056 (1977). A pioneering accomplishment of the Itakura group is that the gene was not from a human source, but instead was entirely synthesized in the laboratory using chemical methods. It is not clear whether the appellants communicated only the results reported in the Polisky publication or whether they communicated the complete claimed invention.

Footnote 12. The patent application indicates that chains as long as 60 amino acids were added, which is hardly a trivial length of polypeptide.

- End of Case -

FULL TEXT OF CASES (USPQ2D)

All Other Cases



In re Deuel (CA FC) 34 USPQ2d 1210 In re Deuel

**U.S. Court of Appeals Federal Circuit
34 USPQ2d 1210**

Decided March 28, 1995

No. 94-1202

Headnotes

PATENTS

1. Patentability/Validity -- Obviousness -- Relevant prior art -- Particular inventions (§ 115.0903.03)

Existence of general method of isolating cDNA or DNA molecules is essentially irrelevant to question of whether specific molecules themselves would have been obvious, in absence of other prior art that suggests claimed DNAs, nor does fact that general process can be conceived in advance for preparing undefined compound mean that claimed specific compound was precisely envisioned and therefore obvious; Board of Patent Appeals and Interferences thus erred by rejecting claims for isolated and purified

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DNA and cDNA molecules encoding heparin-binding growth factors based upon alleged obviousness of method of making molecules, since applied references do not teach or suggest claimed cDNA molecules.

Case History and Disposition:

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Appeal from the U.S. Patent and Trademark Office, Board of Patent Appeals and Interferences; 33 USPQ2d 1445 .

Application for patent filed by Thomas F. Deuel, Yue-Sheng Li, Ned R. Siegel, and Peter G. Milner, serial no. 07/542,232). From decision of the Board of Patent Appeals and Interferences affirming examiner's final rejection of claims, applicants appeal. Reversed.

Attorneys:

G. Harley Blosser and Donald G. Leavit, of Senniger, Powers, Leavitt & Roedel, St. Louis, Mo., for appellants.

Donald S. Chisum, of Morrison & Foerster, Seattle, Wash.; Debra A. Shetka, of Morrison & Foerster, Palo Alto, Calif.; and Robert P. Blackburn, Emeryville, Calif., for amicus curiae The Biotechnology Industry Association and The Bay Area Bioscience Center.

Teddy S. Gron, acting associate solicitor, Albin F. Drost, acting solicitor, and Nancy J. Linck, office of the solicitor, Arlington, Va., for appellee.

Judge:

Before Archer, chief judge, Nies and Lourie, circuit judges.

Opinion Text

Opinion By:

Lourie, J.

Thomas F. Deuel, Yue-Sheng Li, Ned R. Siegel, and Peter G. Milner (collectively "Deuel") appeal from the November 30, 1993 decision of the U.S. Patent and Trademark Office Board of Patent Appeals and Interferences affirming the examiner's final rejection of claims 4-7 of application Serial No. 07/542,232, entitled "Heparin-Binding Growth Factor," as unpatentable on the ground of obviousness under 35 U.S.C. Section 103 (1988). *Ex parte Deuel*, 33 USPQ2d 1445 (Bd. Pat. App. Int. 1993). Because the Board erred in concluding that Deuel's claims 5 and 7 directed to specific cDNA molecules would have been obvious in light of the applied references, and no other basis exists in the record to support the rejection with respect to claims 4 and 6 generically covering all possible DNA molecules coding for the disclosed proteins, we reverse.

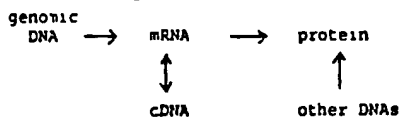
BACKGROUND

The claimed invention relates to isolated and purified DNA and cDNA molecules encoding heparin-binding growth factors ("HBGFs"). 1 HBGFs are proteins that stimulate mitogenic activity (cell division) and thus facilitate the repair or replacement of damaged or diseased tissue. DNA (deoxyribonucleic acid) is a generic term which encompasses an enormous number of complex macromolecules made up of nucleotide units. DNAs consist of four

different nucleotides containing the nitrogenous bases adenine, guanine, cytosine, and thymine. A sequential grouping of three such nucleotides (a "codon") codes for one amino acid. A DNA's sequence of codons thus determines the sequence of amino acids assembled during protein synthesis. Since there are 64 possible codons, but only 20 natural amino acids, most amino acids are coded for by more than one codon. This is referred to as the "redundancy" or "degeneracy" of the genetic code.

DNA functions as a blueprint of an organism's genetic information. It is the major component of genes, which are located on chromosomes in the cell nucleus. Only a small part of chromosomal DNA encodes functional proteins.

Messenger ribonucleic acid ("mRNA") is a similar molecule that is made or transcribed from DNA as part of the process of protein synthesis. Complementary DNA ("cDNA") is a complementary copy ("clone") of mRNA, made in the laboratory by reverse transcription of mRNA. Like mRNA, cDNA contains only the protein-encoding regions of DNA. Thus, once a cDNA's nucleotide sequence is known, the amino acid sequence of the protein for which it codes may be predicted using the genetic code relationship between codons and amino acids. The reverse is not true, however, due to the degeneracy of the code. Many other DNAs may code for a particular protein. The functional relationships between DNA, mRNA, cDNA, and a protein may conveniently be expressed as follows:



Collections ("libraries") of DNA and cDNA molecules derived from various

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species may be constructed in the laboratory or obtained from commercial sources. Complementary DNA libraries contain a mixture of cDNA clones reverse-transcribed from the mRNAs found in a specific tissue source.

Complementary DNA libraries are tissue-specific because proteins and their corresponding mRNAs are only made ("expressed") in specific tissues, depending upon the protein. Genomic DNA ("gDNA") libraries, by contrast, theoretically contain all of a species' chromosomal DNA. The molecules present in cDNA and DNA libraries may be of unknown function and chemical structure, and the proteins which they encode may be unknown. However, one may attempt to retrieve molecules of interest from cDNA or gDNA libraries by screening such libraries with a gene probe, which is a synthetic radiolabelled nucleic acid sequence designed to bond ("hybridize") with a target complementary base sequence. Such "gene cloning" techniques thus exploit the fact that the bases in DNA always hybridize in complementary pairs: adenine bonds with thymine and guanine bonds with cytosine. A gene probe for potentially isolating DNA or cDNA encoding a protein may be designed once the protein's amino acid sequence, or a portion thereof, is known.

As disclosed in Deuel's patent application, Deuel isolated and purified HBGF from bovine uterine tissue, found that it exhibited mitogenic activity, and determined the first 25 amino acids of the protein's N-terminal sequence. Deuel then isolated a cDNA molecule encoding bovine uterine HBGF by screening a bovine uterine cDNA library with an oligonucleotide probe designed using the experimentally determined N-terminal sequence of the HBGF. Deuel purified and sequenced the cDNA molecule, which was found to consist of a sequence of 1196 nucleotide base pairs. From the cDNA's nucleotide sequence, Deuel then predicted the complete amino acid sequence of bovine uterine HBGF disclosed in Deuel's application.

Deuel also isolated a cDNA molecule encoding human placental HBGF by screening a human placental cDNA library using the isolated bovine uterine cDNA clone as a probe. Deuel purified and sequenced the human placental cDNA clone, which was found to consist of a sequence of 961 nucleotide base pairs. From the nucleotide sequence of the cDNA molecule encoding human placental HBGF, Deuel predicted the complete amino acid sequence of human placental HBGF disclosed in Deuel's application. The predicted human placental and bovine uterine HBGFs each have 168 amino acids and calculated molecular weights of 18.9 kD. Of the 168 amino acids present in the two

HBGFs discovered by Deuel, 163 are identical. Deuel's application does not describe the chemical structure of, or state how to isolate and purify, any DNA or cDNA molecule except the disclosed human placental and bovine uterine cDNAs, which are the subject of claims 5 and 7.

Claims 4-7 on appeal are all independent claims and read, in relevant part, as follows:

4. A purified and isolated DNA sequence consisting of a sequence encoding human heparin binding growth factor of 168 amino acids having the following amino acid sequence:

Met Gln Ala . . . [remainder of 168 amino acid sequence].

5. The purified and isolated cDNA of human heparin-binding growth factor having the following nucleotide sequence:

GTCAAAGGCA . . . [remainder of 961 nucleotide sequence].

6. A purified and isolated DNA sequence consisting of a sequence encoding bovine heparin binding growth factor of 168 amino acids having the following amino acid sequence:

Met Gln Thr . . . [remainder of 168 amino acid sequence].

7. The purified and isolated cDNA of bovine heparin-binding growth factor having the following nucleotide sequence:

GAGTGGAGAG . . . [remainder of 1196 nucleotide sequence].

Claims 4 and 6 generically encompass *all* isolated/purified DNA sequences (natural and synthetic) encoding human and bovine HBGFs, despite the fact that Deuel's application does not describe the chemical structure of, or tell how to obtain, any DNA or cDNA except the two disclosed cDNA molecules. Because of the redundancy of the genetic code, claims 4 and 6 each encompass an enormous number of DNA molecules, including the isolated/purified chromosomal DNAs encoding the human and bovine proteins. Claims 5 and 7, on the other hand, are directed to the specifically disclosed cDNA molecules encoding human and bovine HBGFs, respectively.

During prosecution, the examiner rejected claims 4-7 under 35 U.S.C. Section 103 as unpatentable over the combined teachings of

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Bohlen 3 and Maniatis. 4 The Bohlen reference discloses a group of protein growth factors designated as heparin-binding brain mitogens ("HBBMs") useful in treating burns and promoting the formation, maintenance, and repair of tissue, particularly neural tissue. Bohlen isolated three such HBBMs from human and bovine brain tissue. These proteins have respective molecular weights of 15 kD, 16 kD, and 18 kD. Bohlen determined the first 19 amino acids of the proteins' N-terminal sequences, which were found to be identical for human and bovine HBBMs. 5 Bohlen teaches that HBBMs are brain-specific, and suggests that the proteins may be homologous between species. The reference provides no teachings concerning DNA or cDNA coding for HBBMs.

Maniatis describes a method of isolating DNAs or cDNAs by screening a DNA or cDNA library with a gene probe. The reference outlines a general technique for cloning a gene; it does not describe how to isolate a particular DNA or cDNA molecule. Maniatis does not discuss certain steps necessary to isolate a target cDNA, *e.g.*, selecting a tissue-specific cDNA library containing a target cDNA and designing an oligonucleotide probe that will hybridize with the target cDNA.

The examiner asserted that, given Bohlen's disclosure of a heparin-binding protein and its N-terminal sequence and Maniatis's gene cloning method, it would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to clone a gene for HBGF. 6 According to the examiner, Bohlen's published N-terminal sequence would have motivated a person of ordinary skill in the art to clone such a gene because cloning the gene would allow recombinant production of HBGF, a useful protein. The examiner reasoned that a person of ordinary skill in the art could have designed a gene probe based on Bohlen's disclosed N-terminal sequence, then screened a DNA library in accordance with Maniatis's gene cloning method to isolate a gene encoding an HBGF. The examiner did not distinguish between claims 4 and 6 generically directed to all DNA sequences encoding human and bovine

HBGFs and claims 5 and 7 reciting particular cDNAs.

In reply, Deuel argued, *inter alia*, that Bohlen teaches away from the claimed cDNA molecules because Bohlen suggests that HBBMs are brain-specific and, thus, a person of ordinary skill in the art would not have tried to isolate corresponding cDNA clones from human placental and bovine uterine cDNA libraries. The examiner made the rejection final, however, asserting that

[t]he starting materials are not relevant in this case, because it was well known in the art at the time the invention was made that proteins, especially the general class of heparin binding proteins, are highly homologous between species and tissue type. It would have been entirely obvious to attempt to isolate a known protein from different tissue types and even different species.

No prior art was cited to support the proposition that it would have been obvious to screen human placental and bovine uterine cDNA libraries for the claimed cDNA clones. Presumably, the examiner was relying on Bohlen's suggestion that HBBMs may be homologous between species, although the examiner did not explain how homology between species suggests homology between tissue types.

The Board affirmed the examiner's final rejection. In its opening remarks, the Board noted that it is "constantly advised by the patent examiners, who are highly skilled in this art, that cloning procedures are routine in the art." According to the Board, "the examiners urge that when the sequence of a protein is placed into the public domain, the gene is also placed into the public domain because of the routine nature of cloning techniques." Addressing the rejection at issue, the Board determined that Bohlen's disclosure of the existence and isolation of HBBM, a functional protein, would also advise a person of ordinary skill in the art that a gene exists encoding HBBM. The Board found that a person of ordinary skill in the art would have been motivated to isolate such a gene because the protein has useful mitogenic properties, and isolating the gene for HBBM would permit large quantities of the protein to be produced for study and possible commercial use. Like the examiner,

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the Board asserted, without explanation, that HBBMs are the same as HBGFs and that the genes encoding these proteins are identical. The Board concluded that "the Bohlen reference would have suggested to those of ordinary skill in this art that they should make the gene, and the Maniatis reference would have taught a technique for 'making' the gene with a reasonable expectation of success." Responding to Deuel's argument that the claimed cDNA clones were isolated from human placental and bovine uterine cDNA libraries, whereas the combined teachings of Bohlen and Maniatis would only have suggested screening a brain tissue cDNA library, the Board stated that "the claims before us are directed to the product and not the method of isolation. Appellants have not shown that the claimed DNA was not present in and could not have been readily isolated from the brain tissue utilized by Bohlen." Deuel now appeals. 7

DISCUSSION

Obviousness is a question of law, which we review *de novo*, though factual findings underlying the Board's obviousness determination are reviewed for clear error. *In re Vaeck*, 947 F.2d 488, 493, 20 USPQ2d 1438, 1442 (Fed. Cir. 1991); *In re Woodruff*, 919 F.2d 1575, 1577, 16 USPQ2d 1934, 1935 (Fed. Cir. 1990). The examiner bears the burden of establishing a *prima facie* case of obviousness. *In re Rijckaert*, 9 F.3d 1531, 1532, 28 USPQ2d 1955, 1956 (Fed. Cir. 1993); *In re Oetiker*, 977 F.2d 1443, 1445, 24 USPQ2d 1443, 1444 (Fed. Cir. 1992). Only if this burden is met does the burden of coming forward with rebuttal argument or evidence shift to the applicant. *Rijckaert*, 9 F.3d at 1532, 28 USPQ2d at 1956. When the references cited by the examiner fail to establish a *prima facie* case of obviousness, the rejection is improper and will be overturned. *In re Fine*, 837 F.2d 1071, 1074, 5 USPQ2d 1596, 1598 (Fed. Cir. 1988).

On appeal, Deuel challenges the Board's determination that the applied references establish a *prima facie* case of obviousness. In response, the PTO maintains that the claimed invention would have been *prima facie* obvious

over the combined teachings of Bohlen and Maniatis. Thus, the appeal raises the important question whether the combination of a prior art reference teaching a method of gene cloning, together with a reference disclosing a partial amino acid sequence of a protein, may render DNA and cDNA molecules encoding the protein *prima facie* obvious under Section 103.

[1] Deuel argues that the PTO failed to follow the proper legal standard in determining that the claimed cDNA molecules would have been *prima facie* obvious despite the lack of structurally similar compounds in the prior art. Deuel argues that the PTO has not cited a reference teaching cDNA molecules, but instead has improperly rejected the claims based on the alleged obviousness of a method of making the molecules. We agree.

Because Deuel claims new chemical entities in structural terms, a *prima facie* case of unpatentability requires that the teachings of the prior art suggest *the claimed compounds* to a person of ordinary skill in the art. Normally a *prima facie* case of obviousness is based upon structural similarity, *i.e.*, an established structural relationship between a prior art compound and the claimed compound. Structural relationships may provide the requisite motivation or suggestion to modify known compounds to obtain new compounds. For example, a prior art compound may suggest its homologs because homologs often have similar properties and therefore chemists of ordinary skill would ordinarily contemplate making them to try to obtain compounds with improved properties. Similarly, a known compound may suggest its analogs or isomers, either geometric isomers (*cis v. trans*) or position isomers (*e.g.*, *ortho v. para*).

In all of these cases, however, the prior art teaches a specific, structurally-definable compound and the question becomes whether the prior art would have suggested making the specific molecular modifications necessary to achieve the claimed invention. See *In re Jones*, 958 F.2d 347, 351, 21 USPQ2d 1941, 1944 (Fed. Cir. 1992); *In re Dillon*, 919 F.2d 688, 692, 16 USPQ2d 1897, 1901 (Fed. Cir. 1990) (*en banc*) ("structural similarity between claimed and prior art subject matter, . . . where the prior art gives reason or motivation to make the claimed compositions, creates a *prima facie* case of obviousness"), *cert. denied*, 500 U.S. 904 (1991); *In re Grabiak*, 769 F.2d 729, 731-32, 226 USPQ 870, 872 (Fed. Cir. 1985) ("[I]n the case before us there must be adequate support in the prior art for the [prior art] ester/ [claimed] thioester change in structure, in order to complete the PTO's *prima facie*

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case and shift the burden of going forward to the applicant."); *In re Lalu*, 747 F.2d 703, 705, 223 USPQ 1257, 1258 (Fed. Cir. 1984) ("The prior art must provide one of ordinary skill in the art the motivation to make the proposed molecular modifications needed to arrive at the claimed compound.").

Here, the prior art does not disclose any relevant cDNA molecules, let alone close relatives of the specific, structurally-defined cDNA molecules of claims 5 and 7 that might render them obvious. Maniatis suggests an allegedly obvious process for trying to isolate cDNA molecules, but that, as we will indicate below, does not fill the gap regarding the subject matter of claims 5 and 7. Further, while the general idea of the claimed molecules, their function, and their general chemical nature may have been obvious from Bohlen's teachings, and the knowledge that some gene existed may have been clear, the precise cDNA molecules of claims 5 and 7 would not have been obvious over the Bohlen reference because Bohlen teaches proteins, not the claimed or closely related cDNA molecules. The redundancy of the genetic code precluded contemplation of or focus on the specific cDNA molecules of claims 5 and 7. Thus, one could not have conceived the subject matter of claims 5 and 7 based on the teachings in the cited prior art because, until the claimed molecules were actually isolated and purified, it would have been highly unlikely for one of ordinary skill in the art to contemplate what was ultimately obtained. What cannot be contemplated or conceived cannot be obvious.

The PTO's theory that one might have been motivated to try to do what Deuel in fact accomplished amounts to speculation and an impermissible hindsight reconstruction of the claimed invention. It also ignores the fact that claims 5 and 7 are limited to specific compounds, and any motivation that existed was a general one, to try to obtain

a gene that was yet undefined and may have constituted many forms. A general motivation to search for some gene that exists does not necessarily make obvious a specifically-defined gene that is subsequently obtained as a result of that search. More is needed and it is not found here.

The genetic code relationship between proteins and nucleic acids does not overcome the deficiencies of the cited references. A prior art disclosure of the amino acid sequence of a protein does not necessarily render particular DNA molecules encoding the protein obvious because the redundancy of the genetic code permits one to hypothesize an enormous number of DNA sequences coding for the protein. No particular one of these DNAs can be obvious unless there is something in the prior art to lead to the particular DNA and indicate that it should be prepared. We recently held in *In re Baird*, 16 F.3d 380, 29 USPQ2d 1550 (Fed. Cir. 1994), that a broad genus does not necessarily render obvious each compound within its scope. Similarly, knowledge of a protein does not give one a conception of a particular DNA encoding it. Thus, *a fortiori*, Bohlen's disclosure of the N-terminal portion of a protein, which the PTO urges is the same as HBGF, would not have suggested the particular cDNA molecules defined by claims 5 and 7. This is so even though one skilled in the art knew that some DNA, albeit not in purified and isolated form, did exist. The compounds of claims 5 and 7 are specific compounds not suggested by the prior art. A different result might pertain, however, if there were prior art, *e.g.*, a protein of sufficiently small size and simplicity, so that lacking redundancy, each possible DNA would be obvious over the protein. See *In re Petering*, 301 F.2d 676 (CCPA 1962) (prior art reference disclosing limited genus of 20 compounds rendered every species within the genus unpatentable). That is not the case here.

The PTO's focus on known methods for potentially isolating the claimed DNA molecules is also misplaced because the claims at issue define compounds, not methods. See *In re Bell*, 991 F.2d 781, 785, 26 USPQ2d 1529, 1532 (Fed. Cir. 1993). In *Bell*, the PTO asserted a rejection based upon the combination of a primary reference disclosing a protein (*and its complete amino acid sequence*) with a secondary reference describing a general method of gene cloning. We reversed the rejection, holding in part that " [t]he PTO's focus on Bell's method is misplaced. Bell does not claim a method. Bell claims compositions, and the issue is the obviousness of the claimed compositions, not of the method by which they are made." *Id.*

We today reaffirm the principle, stated in *Bell*, that the existence of a general method of isolating cDNA or DNA molecules is essentially irrelevant to the question whether the specific molecules themselves would have been obvious, in the absence of other prior art that suggests the claimed DNAs. A prior art disclosure of a process *reciting a particular compound* or obvious variant thereof as a product of the process is, of course, another matter, raising issues of anticipation under 35 U.S.C. Section 102 as well as obviousness under Section 103. Moreover, where there is prior art that suggests a claimed compound, the existence, or lack thereof, of an enabling process for making that compound is surely a factor

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in any patentability determination. See *In re Brown*, 329 F.2d 1006, 141 USPQ 245 (CCPA 1964) (reversing rejection for lack of an enabling method of making the claimed compound). There must, however, still be prior art that suggests the claimed compound in order for a *prima facie* case of obviousness to be made out; as we have already indicated, that prior art was lacking here with respect to claims 5 and 7. Thus, even if, as the examiner stated, the existence of general cloning techniques, coupled with knowledge of a protein's structure, might have provided motivation to prepare a cDNA or made it obvious to prepare a cDNA, that does not necessarily make obvious a particular claimed cDNA. "Obvious to try" has long been held not to constitute obviousness. *In re O'Farrell*, 853 F.2d 894, 903, 7 USPQ2d 1673, 1680-81 (Fed. Cir. 1988). A general incentive does not make obvious a particular result, nor does the existence of techniques by which those efforts can be carried out. Thus, Maniatis's teachings, even in combination with Bohlen, fail to suggest the claimed invention.

The PTO argues that a compound may be defined by its process of preparation and therefore that a conceived process for making or isolating it provides a definition for it and can render it obvious. It cites *Amgen Inc. v. Chugai*

Pharmaceutical Co. , 927 F.2d 1200, 18 USPQ2d 1016 (Fed. Cir.), *cert. denied* , 502 U.S. 856 (1991), for that proposition. We disagree. The fact that one can conceive a general process in advance for preparing an *undefined* compound does not mean that a claimed *specific* compound was precisely envisioned and therefore obvious. A substance may indeed be defined by its process of preparation. That occurs, however, when it has already been prepared by that process and one therefore knows that the result of that process is the stated compound. The process is part of the definition of the compound. But that is not possible in advance, especially when the hypothetical process is only a general one. Thus, a conceived method of preparing some undefined DNA does not define it with the precision necessary to render it obvious over the protein it encodes. We did not state otherwise in *Amgen* . See *Amgen* , 927 F.2d at 1206-9, 18 USPQ2d at 1021-23 (isolated/purified human gene held nonobvious; no conception of gene without envisioning its precise identity despite conception of general process of preparation).

We conclude that, because the applied references do not teach or suggest the claimed cDNA molecules, the final rejection of claims 5 and 7 must be reversed. See also *Bell* , 991 F.2d at 784-85, 26 USPQ2d at 1531-32 (human DNA sequences encoding IGF proteins nonobvious over asserted combination of references showing gene cloning method and complete amino acid sequences of IGFs).

Claims 4 and 6 are of a different scope than claims 5 and 7. As is conceded by Deuel, they generically encompass all DNA sequences encoding human and bovine HBGFs. Written in such a result-oriented form, claims 4 and 6 are thus tantamount to the general idea of all genes encoding the protein, all solutions to the problem. Such an idea might have been obvious from the *complete* amino acid sequence of the protein, coupled with knowledge of the genetic code, because this information may have enabled a person of ordinary skill in the art to envision the idea of, and, perhaps with the aid of a computer, even identify all members of the claimed genus. The Bohlen reference, however, only discloses a partial amino acid sequence, and thus it appears that, based on the above analysis, the claimed genus would not have been obvious over this prior art disclosure. We will therefore also reverse the final rejection of claims 4 and 6 because neither the Board nor the patent examiner articulated any separate reasons for holding these claims unpatentable apart from the grounds discussed above.

One further matter requires comment. Because Deuel's patent application does not describe how to obtain any DNA except the disclosed cDNA molecules, claims 4 and 6 may be considered to be inadequately supported by the disclosure of the application. See generally *Amgen Inc. v. Chugai Pharmaceutical Co.* , 927 F.2d 1200, 1212-14, 18 USPQ2d 1016, 1026-28 (Fed. Cir.) (generic DNA sequence claims held invalid under 35 U.S.C. Section 112, first paragraph), *cert. denied* , 502 U.S. 856 (1991); *In re Fisher* , 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970) (Section 112 "requires that the scope of the claims must bear a reasonable correlation to the scope of enablement provided by the specification to persons of ordinary skill in the art."). As this issue is not before us, however, we will not address whether claims 4 and 6 satisfy the enablement requirement of Section 112, first paragraph, but will leave to the PTO the question whether any further rejection is appropriate.

We have considered the PTO's remaining arguments and find them not persuasive.

CONCLUSION

The Board's decision affirming the final rejection of claims 4-7 is reversed. *REVERSED*

Footnotes

Footnote 1. For a more extensive discussion of recombinant DNA technology, see *In re O'Farrell* , 853 F.2d 894, 895-99, 7 USPQ2d 1673, 1674-77 (Fed. Cir. 1988); *Amgen Inc. v. Chugai Pharmaceutical Co.* , 927 F.2d 1200, 18 USPQ2d 1016 (Fed. Cir.), *cert. denied* , 502 U.S. 856 (1991).

Footnote 2. Deuel determined that the N-terminal sequence of bovine uterus HBGF is Gly - Lys - Lys - Glu - Lys -

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Pro - Glu - Lys - Lys - Val - Lys - Lys - Ser - Asp - Cys - Gly - Glu - Trp - Gln - Trp - Ser - Val - Cys - Val - Pro.

Footnote 3. European Patent Application No. 0326075, naming Peter Bohlen as inventor, published August 2, 1989.

Footnote 4. Maniatis et al., *Molecular Cloning: A Laboratory Manual*, "Screening Bacteriophage [lambda] Libraries for Specific DNA Sequences by Recombination in *Escherichia coli*," Cold Spring Harbor Laboratory, New York, 1982, pp. 353-361.

Footnote 5. Bohlen's disclosed N-terminal sequence for human and bovine HBBMs is Gly - Lys - Lys - Glu - Lys - Pro - Glu - Lys - Lys - Val - Lys - Lys - Ser - Asp - Cys - Gly - Glu - Trp - Gln. This sequence matches the first 19 amino acids of Deuel's disclosed N-terminal sequence.

Footnote 6. The examiner and the Board apparently used the term "gene" to refer both to natural (chromosomal) DNA and synthetic cDNA. We will use the several terms as appropriate.

Footnote 7. Deuel is supported in its appeal by an *amicus curiae* brief submitted by the Biotechnology Industry Organization and the Bay Area Science Center. Amici urge that, contrary to controlling precedent, the PTO has unlawfully adopted a *per se* rule that a gene is *prima facie* obvious when at least part of the amino acid sequence of the protein encoded by the gene is known in the prior art.

- End of Case -

FULL TEXT OF CASES (USPQ FIRST SERIES)

In re Antonie, 195 USPQ 6 (CCPA 1977)

In re Antonie

(CCPA)

195 USPQ 6

Decided Aug. 18, 1977

No. 76-681

U.S. Court of Customs and Patent Appeals

Headnotes

PATENTS

1. Patentability -- Invention -- In general (§ 51.501)

Court of Customs and Patent Appeals must first delineate invention as whole in determining whether invention as whole would have been obvious under 35 U.S.C. 103; it looks not only to subject matter that is literally recited in claim in question but also to those properties of subject matter that are inherent in subject matter and are disclosed in specification, in delineating invention as whole; just as chemical and its properties are looked to when obviousness of composition of matter claim is examined for obviousness, invention as whole, not some part of it, must be obvious under Section 103.

2. Patentability -- Invention -- In general (§ 51.501)

Controlling question in determining obviousness is simply whether differences between prior art and invention as whole are such that invention as whole would have been obvious.

3. Patentability -- Invention -- In general (§ 51.501)

Standard of 35 U.S.C. 103 is not that it would be obvious for one of ordinary skill in art to try invention; disregard for unobviousness of results of "obvious to try" experiments disregards "invention as a whole" concept of Section 103, and overemphasis on routine nature of data gathering required to arrive at applicant's discovery, after its existence became expected, overlooks last sentence of Section 103.

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4. Patentability -- Change -- In general (§ 51.251)**Patentability -- Invention -- In general (§ 51.501)**

Exception to rule that discovery of optimum value of variable in known process is normally obvious occurs when parameter optimized was not recognized to be result effective variable.

Particular patents -- Contactor Apparatus

Antonie, Rotating Biological Contactor Apparatus, rejection of claims 1-3 reversed.

Case History and Disposition:

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Appeal from Patent and Trademark Office Board of Appeals.

Application for patent of Ronald L. Antonie, Serial No. 331,796, filed Feb. 12, 1973. From decision rejecting claims 1-3, applicant appeals. Reversed; Miller, Judge, concurring in result; Maletz, Judge, with whom Rich, Judge, joins, dissenting with opinion.

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Attorneys:

Arthur H. Seidel, Thomas W. Ehrmann, and Quarles & Brady, all of Milwaukee, Wis., for appellant.

Joseph F. Nakamura (R. D. Edmonds, of counsel) for Commissioner of Patents and Trademarks.

Judge:

Before Markey, Chief Judge, Rich, Baldwin, and Miller, Associate Judges, and Herbert N. Maletz, * Associate Judge, United States Customs Court.

Opinion Text**Opinion By:**

Baldwin, Judge.

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Appeals (board) affirming the rejection of claims 1, 2 and 3 of an application for "Rotating Biological Contactor Apparatus" ¹ as obvious under 35 USC 103 in view of El-Naggar. ² We reverse.

The Invention

Appellant claims a wastewater treatment device in which wastewater is continuously passed through a tank. Semi-immersed contactors (disks) are continuously rotated to aerate their immersed portions and thereby to aerate both microorganisms that grow on the contactors and the wastewater itself. For this discussion, several variables are important in this device. "Throughput" is the volume of wastewater per unit time (gal./day) which the device must treat. "Contactor area" is the total area of the contactors which is exposed to the wastewater as the contactors are rotated (sq. ft.). "Tank volume" is the actual volume of liquid in the tanks in which the contactors rotate (gal.). The ratio of throughput to contactor area (gal./day/sq. ft.) is called the "hydraulic loading." Two concepts of effectiveness of the equipment are important in this discussion. The primary prior art reference uses the term "efficiency" to denote the percent impurity reduction which a given set-up of the device achieves and we shall so use the term. Appellant uses the term "maximum treatment capacity" to denote when a *unit of contactor area* is providing maximum "efficiency" for a given "throughput" or maximum "throughput" for a given "efficiency." It is essential to understand the distinction between "efficiency," a matter of ultimate effectiveness independent of the efficiency of the equipment, and "treatment capacity," a matter of the efficiency or effectiveness of a unit of contactor area. The latter is more properly associated with the normal use of the term "efficiency" denoting maximum result from a limited resource.

Appellant's claimed device has a ratio of tank volume to contactor area of 0.12 gal./sq. ft. ³ Appellant maintains that this ratio is the most desirable or optimum for all set-ups of the device in the sense that using a lower value gives lower "treatment capacity" and using a greater value gives no increase in "treatment capacity," merely increasing costs. Thus, the value is optimum in that it maximizes "treatment capacity" so that the effectiveness of a given contactor is maximized.

The Prior Art

El-Naggar teaches the basic structure of the device claimed by appellant but is silent regarding quantitative design parameters other than to give data on a single example, which data was apparently complete *except for any discussion of "tank volume."* El-Naggar stated the "efficiency" (obviously referring to the purity of the output) could be increased to 95% by increasing the area of the contactor.

The Rejection

The examiner rejected the claims as obvious under 35 USC 103, noting that the basic device in question is old as taught by El-Naggar. While the ratio of tank volume to contactor area of 0.12 gal./sq. ft. is not disclosed in El-Naggar, the examiner reasoned that the disclosure of El-Naggar would make a device with that optimum value obvious. The examiner noted that El-Naggar suggests increasing the "efficiency" (degree of purification) of his device by increasing the contactor area while apparently keeping the "throughput" constant, that is, reducing the "hydraulic loading." The examiner then *assumed* that El-Naggar teaches keeping the tank volume constant while increasing the contactor area.

Thus, the examiner argued that the idea of increasing tank volume to surface area to increase efficiency is taught and that working out the value for optimum efficiency is mere mechanical experimentation. The board accepted the examiner's reasoning.

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Opinion

[1] In determining whether the invention as a whole would have been obvious under 35 USC 103, we must first delineate the invention as a whole. In delineating the invention as a whole, we look not only to the subject matter which is literally recited in the claim in question (the ratio value) but also to those properties of the subject matter which are inherent in the subject matter *and* are disclosed in the specification. In *re Davies*, 475 F.2d 667, 177 USPQ 381 (CCPA 1973). In this case, the invention as a whole is the ratio value of 0.12 *and* its inherent and disclosed property. That property is that the described devices designed with the ratio will maximize treatment capacity regardless of the values of the other variables in the devices. Just as we look to a chemical and its properties when we examine the obviousness of a composition of matter claim, it is this invention *as a whole*, and not some part of it, which must be obvious under 35 USC 103. Cf. In *re Papesch*, 50 CCPA 1276, 315 F.2d 381, 137 USPQ 43 (1963).

[2] The controlling question is simply whether the differences (namely the value of 0.12 and its property) between the prior art and appellant's invention as a whole are such that appellant's invention as a whole would have been obvious. The answer is no. It is impossible to recognize, from the experiment taught by El-Naggar, that "treatment capacity" is a function of "tank volume" or the tank volume-to-contactor area ratio. Recognition of this functionality is essential to the obviousness of conducting experiments to determine the value of the "tank volume" ratio which will maximize treatment capacity. Such functionality can *only be determined* from data representing either efficiency at varying tank volume, fixed throughput, and fixed contactor area or throughput at varying tank volume, fixed efficiency, and fixed contactor area. Each of these experiments represents treatment capacity with fixed contactor area but varying tank volume. This sort of experiment would not be suggested by the teachings of El-Naggar since he was not trying to maximize or control "treatment capacity." The experiments suggested by El-Naggar do not reveal the property which applicant has discovered, and the PTO has provided us with no other basis for the obviousness of the necessary experiments.

[3] The PTO and the minority appear to argue that it would always be *obvious* for one of ordinary skill in the art *to try* varying *every* parameter of a system in order to optimize the effectiveness of the system even if there is no evidence in the record that the prior art recognized that particular parameter affected the result. ⁴ As we have said many times, *obvious to try* is not the standard of 35 USC 103. In *re Tomlinson*, 53 CCPA 1421, 363 F.2d 928, 150 USPQ 623 (1966). Disregard for the unobviousness of the results of "obvious to try" experiments disregards the "invention as a whole" concept of §103, In *re Dien*, 54 CCPA 1027, 371 F.2d 886, 152 USPQ 550 (1967) and In *re Wiggins*, 55 CCPA 1356, 397 F.2d 356, 158 USPQ 199 (1968), and overemphasis on the routine nature of the data gathering required to arrive at appellant's discovery, after its existence became

expected, overlooks the last sentence of §103. In re Saether, 492 F.2d 849, 181 USPQ 36 (CCPA 1974).

[4]In In re Aller, 42 CCPA 824, 220 F.2d 454, 105 USPQ 233 (1955), the court set out the rule that the discovery of an optimum value of a variable in a known process is normally obvious. We have found exceptions to this rule in cases where the results of optimizing a variable, which was known to be result effective, were unexpectedly good. In

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re Waymouth, 499 F.2d 1273, 182 USPQ 290 (CCPA 1974); In re Saether, supra. This case, in which the parameter optimized was not recognized to be a result-effective variable, is another exception. The decision of the board is reversed.

Footnotes

Footnote 1.

Serial No. 331,796, filed February 12, 1973.

Footnote 2. "Method of Treatment of Sewage by Bio-Oxidation and Apparatus Therefor," U.S. Patent No. 3,335,081, issued August 8, 1967.

Footnote 3. Claims 1 and 2 recite "at least about 0.12" while claim 3 recites "about 0.12."

Footnote 4. The precise nature of the El-Naggar experiment and the nature of the data which would result are rendered hopelessly speculative by El-Naggar's total failure to discuss the critical matter of what is done with the volume of the tank. The PTO appears to assume, as a necessary element of its conclusion, that appellant's ratio is the inevitable result of El-Naggar experiment, and that the tank volume is fixed, apparently because El-Naggar does not suggest changing the tank as additional contactor area is supplied. Even if the same tank were used, the actual liquid volume of the tank could change significantly if 1) the tank has a level control, 2) the tank is not extremely large in comparison to the contactors and 3) the volume-to-area ratio of the contactors themselves is significant. Since these assumptions are not unreasonable, there is serious doubt as to the constant volume of the tank.

Whether one would inevitably arrive at the ratio value of 0.12 or above depends on facts which must be read into El-Naggar, (e.g., the volume of the tank) and on assumptions about the kind of motivation (e.g., the degree of "efficiency" which would be sought). All of this involves, at least on this record, mere speculation. Assuming, as the examiner has, that the tank volume is fixed and the natural motivation is to maximize efficiency, if El-Naggar's equipment has a tank volume to contactor area ratio of less than 0.12, and the resulting efficiency is found wanting, increasing the contactor area to increase "efficiency" will lead away from the claimed ratio.

Dissenting Opinion Text

Dissent By:

Maletz, Judge, with whom Rich, Judge, joins, dissenting.

With all due respect, I cannot agree with the majority's interpretation of the El-Naggar patent. El-Naggar discloses the same wastewater treatment apparatus as claimed, except for the specific volume-to-surface ratio of .12 gallons per square foot as recited in the claims. However, El-Naggar generally discloses varying the number of disks (column 3, lines 31-35), the number of concentric cylinders (column 4, lines 27-30), or the length of the cylinders (column 4, lines 61-62) in his apparatus in order to optimize results. Given the basic apparatus of El-Naggar and the concept of varying the number of disks in a tank in order to optimize impurity removal, I believe that it would have been well within the capabilities of the chemical engineer of ordinary skill to determine empirically, by routine experimentation, the optimum design ratio which appellant has determined and recited in his claims. That is, El-Naggar set the way, and appellant's work was what any routineer would have accomplished in following the patent teachings.

Appellant urges that the results which he determined empirically by plotting the effect of volume-to-surface ratio on impurity removal, including the specific, optimum design ratio of .12 gallons per square foot, could not have been predicted from El-Naggar. However, obviousness under 35 USC 103 does not require absolute predictability. In re Kronig, 539 F.2d 1300, 190 USPQ 425 (CCPA 1976), and it is sufficient here that El-Naggar clearly led the way for the routineer to arrive at the claimed apparatus.

I am in substantial agreement with the board's analysis of this case, and I would affirm the board's decision.

Footnote * Judge of the United States Customs Court sitting by designation pursuant to 28 U.S.C. 293(d).

- End of Case -